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Dipyridamole with aspirin is better than aspirin alone in preventing vascular events after ischaemic stroke or TIA

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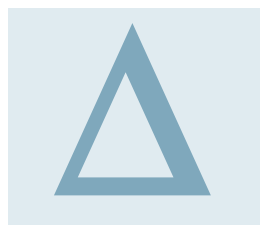
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CHANGE PAGE

Give dipyridamole with aspirin instead of aspirin alone to prevent vascular events after ischaemic stroke or TIA

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Competing interests: I was involved in the cited report on clopidogrel and dipyridamole³ and in planning a trial (of aspirin alone or with these agents) that did not proceed as a potential sponsor wished to modify it. I am on the Antithrombotic Trialists' Collaboration's steering committee and received £500 from Sanofi in 1998 to speak on the Trialists' results at a general practitioners' educational meeting. I'm also a member of the No Free Lunch movement.

Sources of evidence box, references, figure and table are on the longer version on bmj.com

KEY POINTS

- In patients with a prior ischaemic stroke or transient ischaemic attack, adding the antiplatelet drug dipyridamole (modified release formulation, 200 mg twice daily) to aspirin reduces the relative risk of vascular events (stroke, myocardial infarction, or vascular death) by a fifth
- In patients already receiving current secondary preventive treatment, the average annual risk of a vascular event is no more than 5%; adding dipyridamole prevents one further vascular event for every 100 patients treated each year
- Headache may occur in up to a third of people taking dipyridamole but usually settles in one to two weeks

The clinical problem

Strategies to prevent vascular events (stroke, myocardial infarction, or vascular death) after an ischaemic stroke or transient ischaemic attack (TIA) include using aspirin, which is the most widely tested single antiplatelet drug for this purpose.^{1,2} Adding dipyridamole further reduces the risk in patients who have had an ischaemic stroke or transient ischaemic attack.

The evidence for change

Sources of evidence are in the box on bmj.com.¹⁻³

The second European stroke prevention study (ESPS-2) found, in 3299 patients with a prior ischaemic stroke or transient ischaemic attack, that dipyridamole plus aspirin significantly reduced the relative risk of vascular events by about a fifth compared with aspirin alone.^{1,4-6} However, pooled data from previous randomised trials in several thousand patients at high risk of vascular events (about 1800 of whom had a prior ischaemic stroke or transient ischaemic attack) did not find that adding dipyridamole reduced vascular events.^{1,5,6} The contrasting ESPS-2 results were attributed to chance; the very low daily dose (50 mg) of aspirin used compared with previous trials; or the particular daily dose and preparation (400 mg modified release *v* ≤300 mg standard preparation) of dipyridamole used.^{1,7}

The recently published European/Australasian stroke prevention in reversible ischaemia trial (ESPRIT) compared aspirin plus dipyridamole versus aspirin alone in 2739 patients with a prior ischaemic stroke or transient ischaemic attack.⁵ The resulting relative reduction in vascular events was the same as in ESPS-2, and a meta-analysis of all randomised trials comparing the combination with aspirin alone in patients with a prior ischaemic stroke or transient ischaemic attack largely reflected the results of the ESPS-2 and ESPRIT trials.⁵

Assuming a baseline risk of vascular events of 5% a year, the annual risk in the aspirin only arm of ESPRIT (reflecting well the risk in patients already receiving current secondary preventive treatments), the addition of dipyridamole would prevent about 10 vascular events per 1000 patients treated per year.⁵

Neither large trial found an excess of major bleeding in patients allocated the combination compared with aspirin alone. However, both reported a higher rate of premature cessation of treatment in the combination than in the aspirin arm, mainly as a result of adverse effects (particularly dipyridamole induced

headache, which may occur in up to a third of people receiving dipyridamole but usually settles in one to two weeks and might be reduced by dipyridamole dose titration).^{4,5,8}

Barriers to change

Doctors or patients may perceive that the small absolute benefit is not worth while, and adherence may be limited by adverse effects and the difficulties for a predominantly elderly population to take additional medication. As rapid intravenous injection of dipyridamole reduces blood pressure when it is used as a coronary vasodilator in stress echocardiography and thallium imaging, anxieties have been expressed about dipyridamole in patients with ischaemic heart disease.⁷ However, in ESPRIT, long term oral dipyridamole did not affect blood pressure, and the benefits of adding dipyridamole to aspirin were similar in those with and without ischaemic heart disease.^{5,9} Cost may be a barrier, as in the United Kingdom modified release dipyridamole 200 mg twice daily costs £102 (€150; \$200) a patient per year, compared with £5 a patient per year for aspirin 75 mg daily.¹⁰

How should we change our practice?

Ensure first that

- The diagnosis of ischaemic stroke or transient ischaemic attack is correct (which generally requires prompt specialist assessment and appropriate investigations)
- Existing secondary preventive strategies (such as lifestyle advice, aspirin, and reduction in cholesterol and blood pressure) have been or are being considered and used where appropriate
- No reason (such as atrial fibrillation) exists to consider anticoagulants instead of antiplatelet treatment
- The patient is already taking and tolerating aspirin, the most appropriate dose being 75-150 mg daily as higher doses produce more gastrointestinal side effects and lower doses may be less effective.^{1,7}

Then discuss with the patient (or proxy) the likely absolute benefit of adding modified release dipyridamole 200 mg twice daily (that is, on average about a 1 in 100 chance per year of benefiting) versus the potential for adverse effects and the inconvenience of extra pills. Start dipyridamole if the patient wishes; it can be continued long term if tolerated and if no contraindications develop and funding allows.